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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/525,361	03/15/2000	David Mack	A-67860-3/RMS/DAV	9370

20350 7590 12/04/2002

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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	19

DATE MAILED: 12/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/525,361	MACK ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-58* is/are rejected.

7)☒ Claim(s) *48-58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Search Results* .

DETAILED ACTION

1. It is noted that the Art Unit to which this application is assigned has changed from Art Unit 1655 to Art Unit 1634.

2. The Preliminary Amendment filed October 16, 2001, paper no. 12, and the Amendment filed April 22, 2002, paper no. 17, have been entered. The paper and computer readable forms of the Sequence Listing filed October 16, 2001, have been entered. Claims 48-58 are now pending and under consideration.

Election/Restriction

3. Applicant's election with traverse of Group VI in Paper No. 10 is again acknowledged. All claims drawn to non-elected Groups I-V and VII-XIX have now been canceled. All of the pending claims (claims 48-58) are drawn to the invention of elected Group VI.

Priority

4. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

It is noted that while Applicant indicated on pages 1-2 of the transmittal letter dated March 15, 2000 that the instant application is a continuation-in-part of several other applications, Applicant did not request entry of an amendment to the first line of the

specification in that letter or in another paper. An application data sheet has not been filed in the instant application.

5. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

6. It is noted that the claimed invention is a method requiring detection of a polynucleotide that is "at least 75% identical to the nucleic acid sequence disclosed in SEQ ID NO:23" (see independent claim 48). The sequence set forth in the instant application as SEQ ID NO:23 was not disclosed in any of the applications listed in the above-referenced transmittal letter (see paragraph 4). Accordingly, while the amendment to the specification discussed in paragraph 5, above, will be sufficient to perfect applicants' priority claim under 35 USC 120, the instant claims will not be entitled to the filing date of any of the listed applications. Rather, the effective filing date of the instant claims will remain the filing date of the instant application, i.e., March 15, 2000 (see *Hunt Co. v Mallinckrodt Chemical Works*, 177 F.2d 583,587, 83 USPQ 277, 281; MPEP 201.11).

Specification

7. The amendment filed October 16, 2001 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material that is not supported by the original disclosure is as follows. Applicant amended the description of Figure 10 to recite SEQ ID Nos 54, 56, 57, 59, 60, and 61, and concurrently amended the Sequence Listing to add sequences corresponding to these SEQ ID Nos. The new Sequence Listing added by Applicant also includes new SEQ ID Nos 55, 58, and 62, which appear to constitute polypeptides encoded by SEQ ID Nos 54, 57, and 61, respectively. SEQ ID Nos 54-62 were not disclosed in the instant application as filed. It is noted that the sequences added by Applicants' amendment correspond to particular Accession Nos. that were disclosed in Figure 10. However, the Figure does not recite the sequences, and Applicant has not provided, e.g., declaratory evidence that the sequences added to the specification constitute the particular sequences that corresponded to these accession numbers at the time the invention was made. Accordingly, Applicants' amendment introduces new matter into the specification. Applicant is required to cancel the new matter in the reply to this Office Action.

8. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see, e.g., p. 17, p. 21). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

9. The use of the trademark GeneChip™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

10. The title of the invention is not descriptive of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Methods of diagnosing breast cancer.

Claim Objections

11. Claims 48-58 are objected to because of the following informalities: claim 48 is not punctuated so as to clearly indicate that (i) and (ii) are separate method steps. Appropriate correction is required. This objection could be overcome by amending claim 48 to insert "; and" after "...a patient" in the 3rd line of the claim.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 48-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing breast cancer in a human in which increased levels of SEQ ID NO: 23 mRNA or of another mRNA encoding the amino acid sequence of SEQ ID NO: 25, as compared to mRNA levels for these

sequences in a normal human breast tissue sample, are detected in a breast tissue sample of a human patient, does not reasonably provide enablement for methods of diagnosing breast cancer in any type of "patient" using any type of "biological sample," in which "the level of" any type of polynucleotide "encoding a BCH1 polypeptide" is detected, and in which the polynucleotide detected does not encode the amino acid sequence of SEQ ID No: 25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to methods of diagnosing breast cancer in a patient in which a biological sample is obtained from a patient and in which "the level of a polynucleotide encoding a BCH1 polypeptide in the sample" is detected, wherein "the polynucleotide is at least 75% identical to the nucleic acid sequence disclosed in SEQ ID NO: 23." Claim 49 further requires that the polynucleotide "is at least 95% identical to SEQ ID NO: 23," while claim 54 states that 'the polynucleotide is SEQ ID NO: 23." Claims 50-51 further limit the sample type to tissue and breast tissue, respectively. Claims 52-53 require that the sample comprises "isolated nucleic acids," and claim 53 further states that the nucleic acids "are mRNA." Claims 55-56 require that the polynucleotide "is labeled," while claim 57 requires that "the polynucleotide is immobilized on a solid surface." Claim 58 states that "the detection step comprises contacting the sample with a biochip, wherein the biochip comprises the nucleic acid sequence disclosed in SEQ ID NO:23."

The specification discloses two particular BCH1 polynucleotide sequences, SEQ ID Nos 23 and 24, each of which encode the BCH1 polypeptide sequence of SEQ ID NO: 25 (see Figures 32-34 and the descriptions thereof). The specification teaches that a "high level of BCH1" is indicative of poor prognosis in individuals with breast cancer (see p. 6). The specification provides data regarding levels of BCH1 expression in breast cancer tissue samples as compared to normal control samples, and regarding a correlation between high levels of BCH1 expression and estrogen receptor localization. First, the specification provides a comparison of BCH1 expression levels in several breast cancer tissue samples as compared to a panel of controls including two samples of normal breast tissue (see Figure 36). While the data in Figure 36 indicates that BCH1 levels are higher in a few breast tumor samples than in the normal controls, the majority of the breast cancer samples appear to have exhibited levels of BCH1 expression lower than or similar to the normal breast controls. The specification does not provide further analysis of this data, or indicate, e.g., that a particular subtype of breast cancer tissues were found to exhibit consistently higher BCH1 levels than controls. Thus, the data of Figure 36 are insufficient to provide evidence that particular BCH1 levels are diagnostic for breast cancer or indicative of breast cancer prognosis. However, the specification also provides evidence that high levels of BCH1 expression (levels of 4 or 5 on an immunohistochemical scale of 1-5) correlate with estrogen receptor (ER) localization to the cytoplasm (see p. 63). The specification discloses that "signaling through ER to activate most estrogen-responsive genes is believed to require translocation of activated ER to the nucleus," that "high expression of BCH1 is predicted

to correlate with functionally-negative ER," and that "ER- correlates with poor prognosis" (see p. 63). The prior art as exemplified by Hackl et al (Anticancer Research 18(2A):839-842 [3-4/1998]) discloses that ER+ breast cancer patients "show longer disease-free intervals and a better overall survival compared to those who are" ER- (see p. 839). Further, the prior art as exemplified by Reed et al (WO 99/33869 A2 [7/1999]) discloses that an mRNA differing from that disclosed by applicant but encoding the same polypeptide is expressed at increased levels in breast cancer tissues as compared to healthy breast tissues (see Example 1 and SEQ ID NO: 56 of Reed et al; see also paragraph 20 below regarding the alignment of SEQ ID NO: 56 of Reed et al with instant SEQ ID NO: 23). Thus, the combined teachings of the specification and of the prior art provide evidence that over-expression of the BCH1 polypeptide described by applicant as SEQ ID NO: 25 is associated with breast cancer and with poor breast cancer prognosis, and indicate that increased expression of this particular BCH1 polypeptide in a breast tissue sample would be one factor that one of skill in the art would reasonably consider in diagnosis of breast cancer in a human patient. However, it is unpredictable as to whether one of skill in the art could use applicants' invention in a manner reasonably commensurate with the instant claims.

First, with the exception of claims 54 and 58, the instant claims are not limited to polynucleotides encoding the amino acid sequence of SEQ ID NO: 25, but rather encompass polynucleotides encoding numerous different polypeptides. While the claims require a polynucleotide "encoding a BCH1 polypeptide" (see claim 48), the specification discloses that the term "BCH1 polypeptide" encompasses any molecule

that could be considered homologous to the disclosed sequences (as determined by any of a variety of different methods), molecules of longer or short length, polypeptides that are "derivative or variant breast cancer proteins as compared to the wild-type sequence," which derivative/variant molecules may have amino acid substitutions, insertions or deletions "at any residue," covalently modified molecules, etc. (see p. 30-35). Thus, the recitation "BCHI polypeptide" encompasses, at a minimum, thousands of different molecules. Similarly, the recitation of a polynucleotide "at least 75% identical to" SEQ ID NO: 23, or even "at least 95% identical" to SEQ ID NO: 23 (as in claim 49), encompasses a vast number of polynucleotides. The teachings of the specification and of the art provide two different mRNA sequences (instant SEQ ID NO: 23, and SEQ ID NO: 56 of Reed et al) that encode the particular BCH1 polypeptide of instant SEQ ID NO: 25, and whose increased expression is associated with breast cancer in humans. Given this guidance and the high level of skill of one of skill in the relevant art, it would not require undue experimentation for a skilled artisan to identify other mRNA molecules that encode SEQ ID NO: 25 and to practice a method of diagnosing breast cancer comprising detection of the level of expression of such other mRNA molecules. However, with regard to the numerous other polynucleotides encompassed by the claims that do not encode SEQ ID NO: 25, it is unpredictable as to whether one of skill in the art could practice Applicants' invention. Neither the specification nor the prior art provide evidence of the existence of polynucleotides "at least 75%" or "at least 95%" identical to SEQ ID NO: 23 that encode polypeptides other than SEQ ID NO: 25 which are associated with breast cancer. As it is unknown as to whether any such molecules

even exist, it is further unpredictable as to whether any quantity of experimentation would be sufficient to identify additional polynucleotides that would be useful in Applicants' invention. Accordingly, it would require undue experimentation for one of skill in the art to practice the invention as now claimed.

Second, the instant claims are not limited to methods in which mRNA levels are detected, but rather encompass detection of "the level of" any type of polynucleotide. The prior art as exemplified by Pollack et al (Nature Genetics 23:41-46 [9/1999]) does disclose that differences in mRNA levels may be caused by changes in DNA copy number, and that changes in the copy number of some particular genes are known to be associated with breast cancer (see entire reference, particular p. 41). However, neither the specification nor the prior art provide any evidence that alterations in the levels of mRNA molecules encoding SEQ ID NO: 25 (or any other "BCH1 polypeptide") result from changes in gene copy number. It is well known to those of skill in the art that alterations in mRNA levels observed in cancer may occur for a variety of reasons other than changes in gene copy number, such as mutations in regulatory regions that affect transcription, mutations that affect mRNA stability, alterations in expression of transcription factors, etc. Thus, absent evidence of changes in gene copy number, it is unpredictable as to whether one of skill in the art could diagnose breast cancer by detecting changes in copy number of a gene encoding SEQ ID NO: 25 or another BCH1 polypeptide. While the specification and the art would enable a skilled artisan to detect increased mRNA levels as an indicator of breast cancer, it would require undue experimentation to practice applicants' invention with any "polynucleotide."

Third, it is noted that the evidence in the specification and in the prior art with respect to an association between increased levels of SEQ ID NO: 25/mRNAs encoding SEQ ID NO: 25 are limited to findings of altered expression in human breast tissue samples. The teachings of the specification and of the art do not establish any association between SEQ ID NO: 25 and breast cancer in non-human patients. Further, neither the specification nor the art provide evidence that one may diagnose breast cancer by detecting altered expression in other types of biological samples (such as blood, urine, saliva, etc.). Given the lack of guidance in the specification and in the art, it is unpredictable as to whether applicants' invention may actually be practiced successfully in non-human patients and/or with biological samples other than breast tissue samples. Further, while one of skill could conduct further experimentation to determine whether the invention could be employed successfully with other sample types or in other types of patients, the outcome of such experimentation cannot be predicted, and it is unknown as to whether any quantity of experimentation would be sufficient to allow one of skill to use applicants' invention on other sample types and/or in other patient types. Thus, while the combined teachings of the specification and of the art would enable one of skill in the art to practice methods of diagnosing breast cancer in a human in which increased levels of SEQ ID NO: 23 mRNA or of another mRNA encoding the amino acid sequence of SEQ ID NO: 25, as compared to mRNA levels for these sequences in a normal human breast tissue sample, are detected in a breast tissue sample of a human patient, it would require undue experimentation for one

of skill in the art to use applicants' invention in a manner reasonably commensurate with the instant claims.

Regarding claims 50-51, it is noted that while the claims are limited to tissue samples (claim 50)/breast tissue samples (claim 51), the claims encompass diagnosis of breast cancer in non-human patients and detection of polynucleotides other than mRNA, and are not limited to mRNA molecules encoding SEQ ID NO: 25. Regarding claim 53, while the claim is limited to mRNA, it encompasses diagnosis of breast cancer in non-human patients and any type of biological sample, and is not limited to mRNA molecules encoding SEQ ID NO: 25. Regarding claims 54 and 58, while the claims are limited to SEQ ID NO: 23 (a particular molecule encoding SEQ ID NO: 25), the claims encompass diagnosis of breast cancer in non-human patients, detection of polynucleotides other than mRNA, and the use of any type of biological sample.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 48-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48-58 are indefinite because it is unclear as to whether the claims are intended to be drawn to a method of "diagnosing breast cancer in a patient," as recited in the preamble of independent claim 48, or to a method of "detecting the level of a polynucleotide encoding a BCH1 polypeptide" in a sample, as recited in step (ii). The claims do not clearly indicate how the detecting of step (ii) relates to or results in

"diagnosing breast cancer in a patient." For example, is the presence of the polynucleotide indicative of cancer, is the presence of a particular level of polynucleotide indicative of cancer, etc.? Clarification is required.

Claims 48-58 are indefinite over the recitation of the phrase "detecting the level of a polynucleotide encoding a BCH1 polypeptide" in claim 48. It is unclear as to whether the requirement to detect "the level" of a polynucleotide is intended to require, e.g., quantitative or semi-quantitative detection of polynucleotides, whether "the level" could refer to a level of polynucleotide in one cell/tissue relative to another cell/tissue, whether the detection of the presence of any quantity of polynucleotide could be considered to constitute determination of "the level" of that polynucleotide, etc. Clarification is required such that one of skill in the art would be apprised as to what must actually be detected/determined in order to meet the requirements of the claims.

Claims 48-58 are indefinite over the recitation of the phrase "encoding a BCH1 polypeptide" in claim 48, because it is unclear as to how this recitation is intended to further limit the claims. While the specification discloses a particular preferred BCH1 polypeptide (SEQ ID NO: 25), the teachings of the specification indicate that the term "BCH1 polypeptide" may also encompass any molecule that could be considered homologous to the particular sequence disclosed in the specification (as determined by any of a variety of different methods), molecules of longer or short length, polypeptides that are "derivative or variant breast cancer proteins as compared to the wild-type sequence," which derivative/variant molecules may have amino acid substitutions, insertions or deletions "at any residue," covalently modified molecules, etc. (see p. 30-

35). The specification does not indicate that a molecule must have any particular structural or functional property in order to be considered a "BCH1 polypeptide," and the term "BCH1" is not an art recognized term, such that one of skill in the art could rely on the art to provide a clear meaning for this terminology. Accordingly, it is unclear as to how the recitation "encoding a BCH1 polypeptide" is intended to further limit the claims, as compared to the recitation, e.g., "encoding a polypeptide." Clarification is required.

Claims 52-53 are indefinite over the recitation of the phrase "wherein the sample comprises isolated nucleic acids" in claim 52. It is noted that the recitation "the sample" refers to a "biological sample from a patient" (see claim 48, step (i)), not, e.g., to a sample that has been processed in some manner after being obtained from a patient. It is unclear as to whether applicant intended to require a particular type of biological sample (e.g., a sample containing nucleic acids free of other cellular molecules or components, such that the nucleic acids might be considered "isolated"), whether the claims are intended to encompass the use of any type of biological sample removed from a patient (such that the removal of the sample would constitute "isolation" of the nucleic acids from the patient), whether applicant intended to require processing of the biological sample to produce a different type of sample that "comprises isolated nucleic acids," etc.

Claims 55-56 are indefinite over the recitation of the limitation "wherein the polynucleotide is labeled" in claim 55. It is noted that "the polynucleotide" of claim 48, from which claim 55 depends, is a target polynucleotide located in a biological sample (not, e.g., a probe molecule being employed in detection of the target polynucleotide). It

is unclear as to whether this recitation is intended to require the performance of an additional method step (e.g., a step of labeling the polynucleotide), whether this language is intended to indicate that it is a property of the polynucleotide being detected in the sample that it is a labeled polynucleotide, whether applicants intended to require the use of a labeled polynucleotide in detection of the target polynucleotide, etc. Clarification is required.

Claim 56 is indefinite over the recitation of the limitation "the label." There is insufficient antecedent basis for this limitation in the claim.

Claim 57 is indefinite over the recitation of the limitation "wherein the polynucleotide is immobilized on a solid surface." It is noted that "the polynucleotide" of claim 48, from which the instant claim depends, is a target polynucleotide located in a biological sample (not, e.g., a probe molecule being employed in detection of the target polynucleotide). It is unclear as to whether this recitation is intended to require the performance of an additional method step (e.g., a step of immobilizing the polynucleotide contained in the sample), whether this language is intended to indicate that it is a property of the polynucleotide being detected in the sample that it is an immobilized polynucleotide, whether applicants intended to employ an immobilized polynucleotide in detection of the target polynucleotide, etc. Clarification is required.

Claim 58 is indefinite over the recitation of the limitation "the detection step." There is insufficient antecedent basis for this limitation in the claim. This rejection could be overcome by amending claim 58 to recite, e.g., "the detecting" in lieu of "the detection step."

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 48-53 and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al (WO 99/33869 A2 [7/1999]) in view of Khan et al (Electrophoresis 20:223-229 [2/1999]).

Reed et al disclose methods of detecting and diagnosing breast cancer in a patient in which a biological sample is obtained from the patient and in which the presence of a DNA molecule having the sequence of SEQ ID NO: 56 is detected (see entire reference, especially pages 4-5, 26-27). SEQ ID NO: 56 of Reed et al is 95.2% identical to instant SEQ ID NO: 23 (see sequence search results depicting an alignment

of instant SEQ ID NO: 23 with SEQ ID NO: 56 of Reed et al). As SEQ ID NO: 56 of Reed et al encodes the same amino acid sequence as instant SEQ ID NO: 23, it is a property of SEQ ID NO: 56 of Reed et al that it encodes a "BCH1 polypeptide," as required by the claims (see sequence search results, and paragraph 20, below). Reed et al disclose methods in which breast cancer is diagnosed by detecting the level of the polypeptide encoded by SEQ ID NO: 56 in a biological sample from a patient (see page 18). Reed et al teach that SEQ ID NO: 56 was identified by performing cDNA library subtraction using a library prepared from a pool of polyA RNA from breast tumor patients and a library prepared from a pool of polyA RNA from normal human breast specimens (see Example 1, particularly pages 27-29). Reed et al further disclose that SEQ ID NO: 56 is over-expressed in breast tumor tissues and expressed at "low levels" in normal tissues (see Example 1, particularly page 30). However, Reed et al do not disclose detection of levels of SEQ ID NO: 56 in individual patient samples, and do not teach a method in which breast cancer is diagnosed by detecting "the level of" a polynucleotide in "a biological sample from a patient," as required by the claims. Khan et al disclose that human cDNA microarrays may be employed in determining the relative levels of expression of multiple genes in cancer cells simultaneously, and that such microarrays "have the particular advantage that they are readily amenable to the analysis of multiple samples" (see entire reference, particularly p. 224, left column).

In view of the teachings of Kahn et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Reed et al's method of diagnosing breast cancer by detecting the presence of SEQ ID NO: 56

in a patient sample so as to have determined the level of SEQ ID NO: 56 mRNA in a breast tissue sample from a patient using a microarray comprising a probe for specific detection of SEQ ID NO: 56 as well as probes for specific detection of other breast-cancer associated mRNAs (see p. 224-226 of Kahn et al). Reed et al disclose that SEQ ID NO: 56 may be expressed at low levels in normal tissue (see above, and p. 30 of Reed), and thereby suggest that determination of mRNA levels (rather than mere detection of the presence of nucleic acid) may be necessary to differentiate healthy cells from cancerous cells in a sample obtained from a patient. Kahn et al disclose that their microarray method allows for simultaneous analysis of the expression of multiple genes, and facilitates the analysis of multiple samples (see entire reference, particular p. 224). Accordingly, an ordinary artisan would have been motivated to have modified the method of Reed et al so as to have determined the level of SEQ ID NO: 56 mRNA and other breast-cancer associated mRNAs in a sample in order to have differentiated between healthy cells having low level expression of SEQ ID NO: 56 and cancerous cells having increased expression of SEQ ID NO: 56, and in order to have simultaneously detected the levels of expression of other known breast-cancer associated genes, for the advantage of more accurately diagnosing the presence of breast cancer. Further, in view of the teachings of Kahn et al, an ordinary artisan would have been motivated to have made such a modification for the advantage of facilitating the analysis of multiple samples from a patient or patients, for the advantages of convenience and efficiency in analysis of samples.

Regarding claim 49, it is again noted that SEQ ID NO: 56 of Reed et al is 95.2% identical to instant SEQ ID NO: 23 (see sequence search results depicting an alignment of instant SEQ ID NO: 23 with SEQ ID NO: 56 of Reed et al). With respect to claims 50-51, Reed et al disclose the use of breast tumor tissue samples (see, e.g., p. 27 of Reed et al). Regarding claims 52-53 and 55-56, it is a property of the breast tumor tissue samples of Reed et al that they comprise nucleic acids, including mRNA. Kahn et al further disclose processing of biological samples to isolate and fluorescently label RNA and it is a property of the isolated RNA that it comprises isolated mRNA (see p. 224, right column-p. 225, left column). With respect to claim 57, Kahn et al disclose the immobilization of sample RNA on a microarray (see p. 225, left column).

19. Claims 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reed et al (WO 99/33869 A2 [7/1999]) in view of Hackl et al (Anticancer Research 18(2A):839-842 [March-April, 1998])

Reed et al disclose methods of detecting and diagnosing breast cancer in a patient in which a biological sample is obtained from the patient and in which the presence of a DNA molecule having the sequence of SEQ ID NO: 56 is detected (see entire reference, especially pages 4-5, 26-27). SEQ ID NO: 56 of Reed et al is 95.2% identical to instant SEQ ID NO: 23 (see sequence search results depicting an alignment of instant SEQ ID NO: 23 with SEQ ID NO: 56 of Reed et al). As SEQ ID NO: 56 of Reed et al encodes the same amino acid sequence as instant SEQ ID NO: 23, it is a property of SEQ ID NO: 56 of Reed et al that it encodes a "BCH1 polypeptide," as required by the claims (see sequence search results, and paragraph 20, below). Reed

et al disclose methods in which breast cancer is diagnosed by detecting the level of the polypeptide encoded by SEQ ID NO: 56 in a biological sample from a patient (see page 18). Reed et al teach that SEQ ID NO: 56 was identified by performing cDNA library subtraction using a library prepared from a pool of polyA RNA from breast tumor patients and a library prepared from a pool of polyA RNA from normal human breast specimens (see Example 1, particularly pages 27-29). Reed et al further disclose that SEQ ID NO: 56 is over-expressed in breast tumor tissues and expressed at "low levels" in normal tissues (see Example 1, particularly page 30). However, Reed et al do not disclose detection of levels of SEQ ID NO: 56 in individual patient samples, and do not teach a method in which breast cancer is diagnosed by detecting "the level of" a polynucleotide in "a biological sample from a patient," as required by the claims. Hackl et al disclose that RT-PCR may be used to semiquantitatively determine levels of estrogen receptor (ER) and progesterone receptor (PgR) mRNA in breast tumor tissue samples obtained from patients (see entire reference, especially page 839, right column and page 840, left column). Hackl et al further teach that their mRNA detection method is more sensitive than methods of detecting protein and allows detection of ER and PgR mRNA in some instances when protein is not detected (see entire reference, especially p. 840, right column and page 841, left column).

In view of the teachings of Hackl et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Reed et al's method of diagnosing breast cancer by detecting the presence of SEQ ID NO: 56 in a patient sample so as to have determined the level of SEQ ID NO: 56 mRNA in a

breast tissue sample from a patient using the semi-quantitative RT-PCR method of Hackl et al. Reed et al disclose that SEQ ID NO: 56 may be expressed at low levels in normal tissue (see above, and p. 30 of Reed), and thereby suggest that quantification of mRNA levels (rather than mere detection of the presence of nucleic acid) may be necessary to differentiate healthy cells from cancerous cells in a sample obtained from a patient. Accordingly, an ordinary artisan would have been motivated to have modified the method of Reed et al so as to have determined the level of SEQ ID NO: 56 mRNA in a sample in order to have differentiated between a healthy cell having low level expression and a cancerous cell having increased expression, for the advantage of more accurately diagnosing the presence of breast cancer.

Additionally, in view of the teachings of Hackl et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified Reed et al's method of diagnosing breast cancer by determining the level of SEQ ID NO: 56-encoded polypeptide in a patient sample so as to have determined the level of SEQ ID NO: 56 mRNA in a breast tissue sample from a patient (rather than the level of SEQ ID NO: 56-encoded polypeptide) using the semi-quantitative RT-PCR method of Hackl et al. Hackl et al disclose that RT-PCR of mRNA allows for more sensitive detection of the level of expression of a target molecule of interest that methods of detecting/quantitating protein, such as those taught by Reed et al at page 18. Accordingly, an ordinary artisan would have been motivated to have modified the method of Reed et al for the advantage of improved sensitivity in detecting the level of expression of SEQ ID NO: 56.

Regarding claim 49, it is again noted that SEQ ID NO: 56 of Reed et al is 95.2% identical to instant SEQ ID NO: 23 (see sequence search results depicting an alignment of instant SEQ ID NO: 23 with SEQ ID NO: 56 of Reed et al). With respect to claims 50-51, both Reed et al and Hackl et al disclose the use of breast tumor tissue samples (see, e.g., p. 27 of Reed et al; p. 839, right column of Hackl et al). Regarding claims 52-53, it is a property of the breast tumor tissue samples of Reed et al and Hackl et al that they comprise nucleic acids, including mRNA. Hackl et al further disclose processing of biological samples to isolate RNA and amplify mRNA (see p. 839, right column and p. 840, left column), and it is a property of the isolated RNA of Hackl et al that it comprises isolated mRNA.

Conclusion

20. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Sequence search results are cited to show the sequence identity shared between SEQ ID NO: 56 of Reed et al and instant SEQ ID NO: 23. Start and stop codons of the BCH1 open reading frame are boxed, as is the codon encoding amino acid 51, which contains a silent mutation.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers

for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
November 29, 2002